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ROLE OF NO IN THE REGULATION OF SYSTEMIC AND RENAL HEMODYNAMICS FOLLOWING HEMORRHAGIC SHOCK IN THE RAT

BY

W. LIEBERTHAL, A. THOMPSON, AND C.R. VALERI

NAVAL BLOOD RESEARCH LABORATORY
BOSTON UNIVERSITY SCHOOL OF MEDICINE
615 ALBANY STREET
BOSTON, MA 02118

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ABSTRACT

The systemic and renal hemodynamic responses to NO inhibition with L-NAME were compared in both normotensive, normovolemic rats and in rats following acute hemorrhagic hypotension. Mean arterial blood pressure (MAP) increased in normovolemic as well as in hemorrhaged, hypotensive rats. Systemic vascular resistance (SVR) also increased in both groups but the increase was greater in normotensive rats (104±11%) than hypotensive rats (64±14%). Renal vascular resistance (RVR) also increased more in normotensive rats (189±20%) than hypotensive rats (102±19%)($p<0.05$). GFR was markedly reduced by L-NAME in normovolemic rats (from 3.0±0.1 to 2.1±0.1 ml/min/300g)> In striking contrats GFR but increased in hemorrhaged rats following L-NAME (from 1.8±0.2 to 2.5±0.2 ml/min/300g. In summary, the L-NAME-induced increase in vascular resistance is markedly reduced following hemorrhage suggesting that NO production or availability is reduced. However, NO production continues in the hemorrhaged rat and contributes substantially to the hypotension and functional renal insufficiency associated with acute severe volume depletion.

KEY WORDS: nitric oxide, L-NAME, hemorrhage,shock, blood pressure renal function, GFR, systemic vascular esistance, renal vascular resistance,

INTRODUCTION

Nitric oxide (NO) produced by the constitutively expressed NO sythase in endothelial cells (eNOS) diffuses into the underlying vascular smooth muscle layer where it induces vasodilation (1). This basal endothelial production of NO has been demonstrated to play an important role in modulating systemic and intrarenal vascular tone *in vivo* by maintaining tonic vasodilation (2,3,4,5,6). In normal animals, examined under acute experimental conditions in both the conscious (2,3,7) as well as the anesthetized state (4,6,8), the administration of NO inhibitors results in marked hypertension, and a fall in renal blood flow and GFR. In septic shock, the production of NO is increased above normal levels due to the synthesis of the inducible form of nitric oxide synthase (iNOS) present in vascular smooth muscle, macrophages,and other cells (1,4,9).

The purpose of this study was to compare the systemic and renal hemodynamic effects of NO inhibition in normovolemic and hemorrhaged rats to elucidate the hemodynamic role of NO following severe volume depletion which remains incompletely defined.

We provide novel data indicating that the increase in vascular resistance with NO inhibition is far greater in normovolemic than in acutely hemorrhaged rats. This data suggests that constitutive production of NO falls with acute volume depletion. We also demonstrate that NO production, though reduced, still contributes substantially to the hyopotension as well as the functional renal insufficiency associated with acute volume depletion.

METHODS

1. Surgical procedure: Male Sprague-Dawley rats, weighing between 300 and 400g, were used for all experiments. Rats were fed regular Purina rat chow (Purina Mills, Chicago, IL) and allowed free access to water. Anesthesia was induced with an intraperitoneal injection of pentobarbital sodium (5 mg/100g body wt) and was then maintained with a constant intravenous infusion of pentobarbital sodium (91 mg/min) throughout the study as previously described (10). Rats were placed on a thermostatically controlled heated table. Body temperature was monitored via a temperature probe in the carotid artery and maintained between 36 and 38°C. A tracheotomy was performed with the use of polyethylene (PE-240) tubing, and both femoral arteries were cannulated with PE-50 tubing, one for blood pressure monitoring and the other for blood sampling. A bladder catheter (PE-90) was placed via a suprapubic incision for urine sampling. The right internal jugular vein was cannulated with two PE-50 catheters. Inulin, PAH and pentobarbital sodium were infused via one catheter. The other two intravenous catheters were used for the infusion of Nw-nitro-L-arginine methyl ester (L-NAME) (Sigma, St Louis, MO.) or its vehicle. The right atrium was catheterized via the left jugular vein with PE-20 tubing and used for cardiac output measurements as described below (10).

Cardiac output was measured with a Cardiomax II-R instrument (Columbus Instruments Corp., Columbus, OH.) using the thermodilution technique as previously described (13). The right carotid artery was cannulated with a thermistor-catheter

combination for measurement of thermodilution cardiac output curves. A French #1.5 thermosensitive microprobe (Columbus Instruments Inc., Columbus, OH) was placed through a sheath of PE-90 tubing and placed into the right carotid artery. The microprobe was advanced along the right carotid artery until resistance was provided by the wall of the aorta at which point the probe was withdrawn by 1/16 of an inch. The PE-50 sheath was then withdrawn and the probe tied in place. Using this technique, the tip of the probe was positioned in the aortic arch just distal to the aortic valve.

Cardiac output was measured by injecting 200ml of cold injectate solution (dextrose water at 20±2°C) via the left jugular vein using a Hamilton syringe. Within 10-15 seconds, a read out of cardiac output (CO), stroke volume and heart rate was obtained. The determination of CO by this method is dependent on an integration of the curve of the time taken for cold solution to reach the temperature sensitive probe in the aortic arch across the pulmonary circulation. Stroke volume is calculated by the Cardiomax-IIR from the measured cardiac output and heart rate. The Cardiomax II-R also provided a constant read out of heart rate and mean arterial pressure via the femoral artery catheter and body temperature via the temperature sensitive probe placed in the aortic arch (10).

Glomerular filtration rate (GFR) and effective renal plasma flow were determined by the renal clearance of inulin-carboxyl [Carboxyl-^{14}C] and aminohippuric acid P-[glycyl-2-^{3}H] respectively (New England Nuclear, Boston, MA). The ^{14}C-inulin was infused at a

rate of 0.06uCi/min and the ^{3}H-PAH at a rate of 0.23uCi/min. Blood samples, obtained at the midpoint of each clearance period were centrifuged and 5ml samples of plasma and urine were added separately to 5ml liquid scintillation fluid and counted for 10 minutes in a liquid scintillation counter (10).

The vials containing both ^{14}C and ^{3}H were counted in a Packard Tri-carb (1600TR) liquid scintillaton analyzer. In order to separate the spectra of the two radionucleotides, the technique of full spectrum dual disintegrations per minute (DPM) counting was used (10).

Experimental Protocols

1) Effect of L-NAME in normotensive, normovolemic rats. After surgical preparation of the rats as outlined above, an infusion of inulin and PAH was begun. After an equilibration period of thirty minutes, three fifteen minute baseline urine collections ("baseline period") were obtained for measurement of inulin and PAH clearance. Blood pressure was monitored continuously throughout this period. Then an infusion of L-NAME was begun. After a thirty minute equilibration period, three fifteen minute clearances were obtained ("L-NAME period"), during which measurement of blood pressure and determinations of inulin and PAH clearances were repeated. Duplicate determinations of cardiac output, were made during the middle of each period ("baseline" and "L-NAME) and the duplicate results averaged. In control experiments the vehicle for L-NAME was infused intead of L-NAME.

2) Effect of L-NAME during hemorrhagic hypotension.

After three fifteen minute urine collections ("baseline period") for inulin and PAH clearance determination, and blood pressure monitoring, rats were subjected to hemorrhage. Whole blood (20 ml/kg body wt) was removed through the femoral arterial catheter at a rate of 1 ml/min. After a 45-min equilibration period, two twenty minute clearances ("posthemorrhage period") were obtained. After this an infusion of L-NAME was begun. After a thirty minute equilibration period three fifteen minute clearances ("L-NAME period") were obtained. Duplicate determinations of cardiac output were made during the middle of each period ("baseline", post-hemorrhage" and L-NAME") and the duplicate results averaged. In control experiments the L-NAME vehicle was administered instead of L-NAME.

Dose of L-NAME: L-NAME was infused at a dose of 0.12 mg/kg/min. In control experiments the vehicle for L-NAME (5g/100ml dextrose water) was infused at a rate of 10ml/min.

Calculations

GFR and PAH clearances were calculated with standard formulas. Renal plasma flow (RPF) was calculated from the clearance of PAH assuming a PAH extraction of 80% (11). Renal blood flow was calculated as RPF/(1 - hematocrit). SVR was calculated by dividing mean arterial blood pressure (MAP) by cardiac output (CO) and RVR was calculated by dividing MAP by renal blood flow.

Statistics

The measurements of GFR and RPF obtained during the triplicate clearances obtained during each period were averaged.

All data are expressed as mean ± SE. All comparisons of two groups were made with the Student's test. All comparisons of more than two groups were made using analysis of variance (ANOVA) followed by the Scheffe test. A p value of <0.05 was considered significant.

RESULTS

1. Effects of L-NAME in normovolemic rats.

L-NAME increased MAP from 111±2 to 142±3mmHg ($p<0.05$)(Table 1). Cardiac output fell from 99±5 to 59±3.1 ml/min/300g ($p<0.05$) due to a decrease in both stroke volume and heart rate. Systemic vascular resistance (SVR) increased following L-NAME from 1.23±0.06 to 2.47±0.14 mmHg/ml/min/300g ($p<0.05$)(Table 1).

L-NAME reduced GFR from 3.0±0.1 to 2.1±0.1 ml/min/300g ($p<0.05$) and renal plasma flow from 10.1±0.5 to 4.9±0.4ml/min/300g ($p<0.05$) while the filtration fraction increased from from 30±1 to 43±2% ($p<0.05$). L-NAME increased RVR from 5.8±0.3 to 16.6±1.2 mmHg/ml/min/300g ($p<0.05$)(Table 1).

The hematocrit was 48±1% during the baseline period and was unchanged by L-NAME (46±1.0%) (p=NS)

2. Effects of acute hemorrhage

In rats subjected to acute hemorrhage, MAP fell from 114±2 to 62±1mmHg ($p<0.05$)(Table 2). Cardiac output fell from 96±3 to 61±4 mmHg/ml/min/300g ($p<0.05$) due to a fall in stroke volume while heart rate increased (Table 2). GFR renal plasma and blood flow both fell following hemorrhage (Table 2). The hematocrit fell from 47±1 to 35±1% ($p<0.05$).

3. Effects of L-NAME administered after acute hemorrhage

MAP rose following L-NAME administration to 91±4mmHg, a value that remained below the baseline (prehemorrhage) value (Table 2). The increase in MAP was not associated with any alteration in cardiac output. Systemic vascular resistance increased from 1.09±0.06 to 1.74±0.13 mmHg/ml/min/300g ($p<0.05$)(Table 2).

GFR rose with L-NAME from 1.8±0.2 to 2.5±0.2ml/min/300g, a level numerically lower but statistically comparable to the baseline (prehemorrhage) value (Table 2). Renal plasma flow increased following L-NAME to a lesser extent than GFR so that the filtration fraction rose from 26±2 to 38±2% (Table 2). L-NAME increased RVR from 5.1±0.4 to 10.1±0.8 mmHg/ml/min/300g ($p<0.05$)(Table 2).The hematocrit fell following hemorrhage from 47±0.5% to 35±0.6% ($p<0.05$) and then fell slightly further following L-NAME (from 35±5 to 32±0.7% ($p<0.05$)).

4. Comparison of L-NAME induced changes in systemic and renal hemodynamics and function in normovolemic and hypovolemic rats.

The percent increase in MAP above baseline values was considerably higher in hypotensive rats (47±7%) than normotensive rats (27±2%)($p<0.05$) (Figure 1). While L-NAME resulted in a 30±3% fall in GFR in normovolemic animals. GFR was increased by 46±14% following hemorrhage (Figure 2). RBF fell with L-NAME treatment in normotensive rats by 53±4% while there was no change in RBF in hypotensive rats (Figure 3).

SVR increased to a greater extent with L-NAME in normotensive compared to hypotensive rats. This was true both for absolute increases in SVR (normovolemic rats: 1.24±0.12 mmHg/ml/min/300g versus hemorrhaged rats 0.65mmHg/ml/min/300g($p<0.05$)), as well as for the percent increase in SVR (normotensive rats 104±11% versus hemorrhaged rats 64±14% ($p<0.05$)) (Figure 4).

RVR also increased to a greater extent with L-NAME in normotensive compared to hypotensive rats. The absolute increases

in RVR in normotensive rats was 10.8±1.1 mmHg/ml/min/300g compared to an increase of 5.5±1.0 mmHg/ml/min/300g in hypotensive rats ($p<0.05$). The percent increase in RVR in normotensive rats was 189±20% compared to 102±19% in hypotensive rats ($p<0.05$)(Figure 4).

The percent increase in RVR (189±20%) was greater than the increase in SVR (104±11%) in normovolemic rats ($p<0.05$). However, the percent increase in RVR (102±19%), though numerically higher was not significantly different from the increase in SVR (64±14%) in hypotensive rats (p=NS)(Figure 4).

5. Control experiments

In the control group of normotensive rats that received the L-NAME vehicle instead of L-NAME there was no change in systemic or renal hemodynamics (Table 3). Administration of the L-NAME vehicle to rats subjected to hemorrhage also did not alter either systemic or renal hemodynamics (Table 4).

DISCUSSION

We have demonstrated that in normovolemic and normotensive Sprague-Dawley rats, NO inhibition with L-NAME causes systemic vasoconstriction and a resultant elevation in MAP well into the hypertensive range (Table 1). However, MAP does not increase in proportion to the increase in peripheral resistance because of an associated profound fall in cardiac output (Table 1).This fall in cardiac output in response to NO inhibition has been ascribed to a reflex baroreceptor response to the hypertension (3). L-NAME also causes substantial intrarenal vasoconstriction and a fall in renal plasma flow and blood flow (Table 1). GFR falls to a relatively greater extent than plasma flow so that filtration fraction increases (Table 2). These systemic and renal hemodynamic effects of NO inhibition in normovolemic animals are comparable to those previously reported in both anesthetized (4,6,8) and conscious animals (2,3,7).

We have also shown that in hemorrhaged, hypotensive rats, MAP is also increased by L-NAME to levels slightly below baseline values (Table 2). Comparable results were described by our group in a previous study using L-NMMA as an NO synthase inhibitor (11). However, in the present study, additional data (measurements of cardiac output and calculations of systemic vascular resistance (SVR)) has enabled us to demonstrate for the first time that the increase in SVR induced by L-NAME is substantially greater in normovolemic than hypovolemic rats (Figure 4). These findings indicate that NO production is substantially reduced during hypotension following acute volume depletion.

However, NO clearly continues to be produced following hemorrhage in amounts that contribute substantially to the hypotension associated with the acute hypovolemic state. We hypothesize that the reduction in NO reduction during acute hypotension is likely due to a diminution in shear stress, a well known regulator of eNOS activity and NO release by endothelial cells (12). Thus the response of the NO system to hypovolemic shock is quite different to the increased in NO production associated with sepsis (9).

One of the other striking findings of this study is that while L-NAME decreases GFR in the normotensive group, GFR is increased in hypotensive rats to a level comparable to baseline, prehemorrhage values (Table 2, Figure 2). These data indicate that continued NO production contributes to the "pre-renal" or functional acute renal failure associated with severe volume depletion.

The increase in GFR observed following NO inhibition in hypotensive rats could potentially be due to a proportionately greater degree of vasoconstriction in the systemic as opposed to the intrarenal vasculature with a resultant increase in the proportion of the cardiac output distributed to the kidney. However, we demonstrate in this study that the increased in SVR with L-NAME in the hemorrhaged rat (64±14%) was no greater than the increase in RVR (102±19%)(p=NS) (Figure 4). Thus, the increase in GFR following NO inhibition in the hemorrhaged rat must be due to hemodynamic alterations within the kidney.

The different response of GFR to L-NAME in normotensive and hypotensive rats is due to a number of interacting factors. Firstly, the proportional increase in perfusion pressure following L-NAME is substantially greater in the hypotensive rat (47±7% above control) than in normotensive rats (27±2% above control)($p<0.05$)(Figure 1). This difference is is due to the fact that cardiac output does not fall with L-NAME in the hypotensive rat as in the normotensive rat, presumably because baroreceptor reflexes are not activated in the range of MAP elevation that occurs in hypotensive animals.

Secondly, the increase in RVR following L-NAME in hemorrhaged rats is substantially less marked in than in normovolemic rats (Figure 4). The most likely explanation for this observation is that the renal autoregulatory response to the L-NAME induced increase in MAP (13) is likely to be far greater in the normotensive rats (in which perfusion pressure is increased by L-NAME within the entire autoregulatory range) than in hypotensive rats given L-NAME (in which MAP is increased to a level just at the lower limits of the the autoregulatory response in rats (~95mmHg)) (2).

Thirdly, in normotensive rats RBF falls profoundly in response to L-NAME (by 53%), while in hypotensive rats RBF is unchanged (Figure 3) suggesting that the L-NAME induced increase in perfusion pressure is balanced by the increase in RVR in the hypotensive rats.

Thus, NO potentiates the functional renal failure of acute hemorrhage in the absence of any change in RBF, by altering

intrarenal hemodynamics. NO produced in the hypotensive state could theoretically potentiate the reduction in GFR either by reducing intraglomerular capillary pressure, by decreasing the glomerular ultafiltration coefficient or by a combination of these two effects.

The results of this study may provide some practical insights into the vasoactive effects of purified and modified preparations of stroma free hemoglobin (SFH) solutions which are being developed for therapeutic use in humans as potential blood substitutes (5,14,15). Hemoglobin, reduces NO availability, but, unlike L-NAME acts by binding NO molecule rather than by reducing NO production (16). Interestingly, our group (5) as well as other investigators (15) have reported that the effects of SFH administration to animals following acute hemorrhage are comparable to those of L-NAME in that blood pressure and GFR are both increased. We have provided evidence in the same study (5) that these hemodynamic effects are due, at least in part,to hemoglobin-induced inactivation of NO.

CONCLUSIONS

Our data suggest that while constitutive NO production is markedly reduced following acute hemorrhage, NO production continues despite the severe volume depletion and contributes substantially to the associated hypotention. Furthermore, the fall in GFR associated with acute volume depletion is alo potentiated by hemodynamic effects of continued no production NO within the renal circulation.

ACKNOWLEDGEMENTS

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TABLE 1

Systemic and renal hemodynamic effects of nitric oxide inhibition with L-NAME on in normotensive, normovolemic rats

	Baseline Period	L-NAME Period
Systemic Hemodynamics		
Mean arterial pressure (mmHg)	111±2	142±3*
Cardiac output (ml/min/300g)	99±5	59±3*
Stroke volume (ml/min/300g)	257±15	166±9 *
Heart rate (beats/minute)	385±14	347±12*
Systemic vascular resistance (mmHg/ml/min/300g)	1.23 ± 0.06	2.47 ± 0.14*
Renal Hemodynamics		
Glomerular filtration rate (ml/min/300g)	3.0 ± 0.1	2.1 ± 0.1*
Renal plasma flow (ml/min/300g)	10.1 ± 0.4	4.9 ± 0.4*
Renal blood flow (ml/min/300g)	19.5 ± 0.9	9.1 ± 0.7*
Filtration fraction (%)	30 ± 1	43 ± 2*
Renal vascular resistance (mmHg/ml/min/300g)	5.8 ± 0.3	16.6 ± 1.2*

n=11

*=p<0.05 compared to baseline period.

TABLE 2

Systemic and renal hemodynamic effects of nitric oxide inhibition with L-NAME in rats following hemorrhagic hypotension

	Baseline Period	Post-Hemorrhage Period	L-NAME Period
Systemic Hemodynamics			
Mean arterial pressure	114 ± 2	62 ± 2*	91 ± 4*†
Cardiac output (ml/min/300g)	96±3	61±4*	55±4 *
Stroke volume (ml/min/300g)	257±9	158±10*	142±13*
Heart rate (beats/min)	368±12	395 ± 4*	380±12
Systemic vascular resistance (mmHg/ml/min/300g)	1.19 ± 0.04	1.09 ± 0.06	1.74 ± 0.13*†
Renal Hemodynamics			
Glomerular filtration rate (ml/min/300g)	3.0 ± 0.2	1.8 ± 0.2*	2.5 ± 0.2†
Renal plasma flow (ml/min/300g)	10.7 ± 0.9	7.3 ± 0.7*	6.5 ± 0.6*
Renal blood flow (ml/min/300g)	19.1 ± 1.9	11 ± 1.0*	9.9 ± 0.9*
Filtration fraction (%)	29 ± 1.0	26 ± 2*	38 ± 2*†
Renal vascular resistance (mmHg/ml/min/300g)	6.8 ± 0.9	5.1 ± 0.4*	10.1 ± 0.8*†

n=10

*=p<0.05 compared to baseline period; †=p<0.05 compared to post hemorrhage period

TABLE 3

Systemic and renal hemodynamic effects of the L-NAME vehicle in normotensive, normovolemic rats

	Baseline	L-NAME vehicle
Mean arterial pressure (mmHg)	114± 2	113 ± 3
Cardiac output (ml/min/300g)	93 ± 7	88 ± 5
Glomerular filtration rate (ml/min/300g)	3.0 ± 0.2	3.1 ± 0.3
Renal plasma flow (ml/min/300g)	9.3 ± 0.6	8.5± 0.4
Renal blood flow (ml/min/300g)	17.4 ± 1.2	15.6 ± 0.9
Filtration fraction (%)	34 ± 1	36 ± 2
Vascular resistance (mmHg/ml/min.300g)		
Systemic	1.26 ± 0.12	1.29 ± 0.08
Renal	6.7 ± 0.7	7.3 ± 0.5

n= 5

TABLE 4

Systemic and renal hemodynamic effects of the L-NAME vehicle in rats following hemorrhagic hypotension

	Post hemorrhage	L-NAME vehicle
Mean arterial pressure (mmHg)	62±2	61±4
Cardiac output (ml/min/300g)	68±9	66±7
Glomerular filtration rate (ml/min/300g)	1.7±0.1	1.8±0.1
Renal plasma flow (ml/min/300g)	7.0 ± 0.3	7.0 ± 0.2
Renal blood flow (ml/min/300g)	10.5±0.4	10.2±0.3
Filtration fraction (%)	27 ± 2	28 ± 1
Vascular resistance (mmHg/ml/min/300g)		
Systemic	1.00±0.20	0.85±0.11
Renal	5.9±0.2	5.8±0.4

n= 5

LEGENDS

Figure 1

Comparison of the percent increase in MAP induced by L-NAME in normovolemic and hypotensive rats

*=p<0.05 compared to pre-LNAME (baseline) period

†=p<0.05 compared to normovolemic rats

Normotensive rats n=11; hypotensive rats n=10

Figure 2

Comparison of the percent change in GFR induced by L-NAME in normovolemic and hypotensive rats

*=p<0.05 compared to pre-LNAME (baseline) period

†=p<0.05 compared to normovolemic rats

Normotensive rats n=11; hypotensive rats n=10

Figure 3

Comparison of the percent change in RBF induced by L-NAME in normovolemic and hypotensive rats

*=p<0.05 compared to pre-LNAME (baseline) period

†=p<0.05 compared to normovolemic rats

Normotensive rats n=11; hypotensive rats n=10

Figure 4

Comparison of the percent change in SVR and RVR induced by L-NAME in normovolemic rats (stippled bar) and hypotensive rats (cross hatched bar)

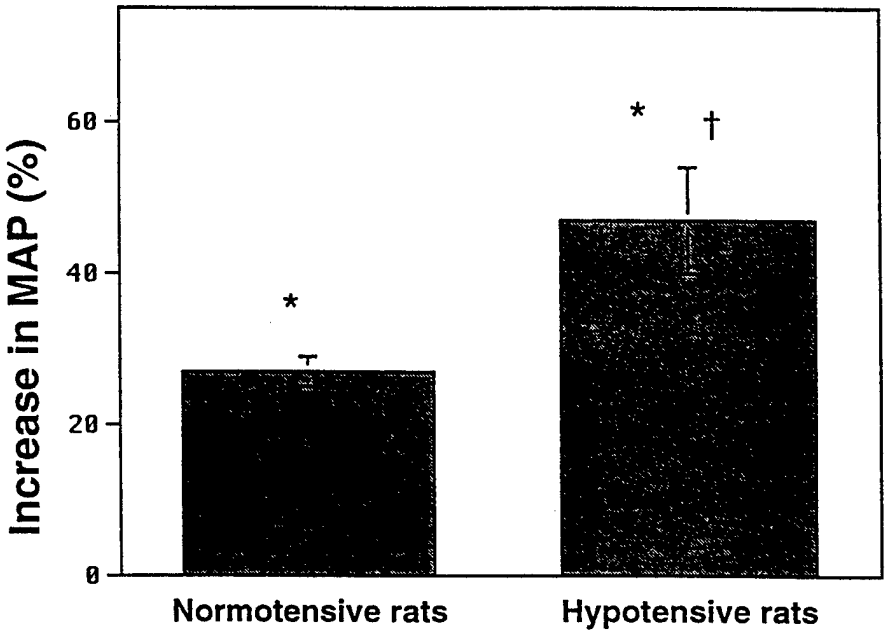
*=p<0.05 compared to SVR in normovolemic animals

†=p<0.05 compared to SVR in normovolemic animals

¶=p<0.05 compared to RVR in hypotensive animals

Normotensive rats n=11; hypotensive rats n=10

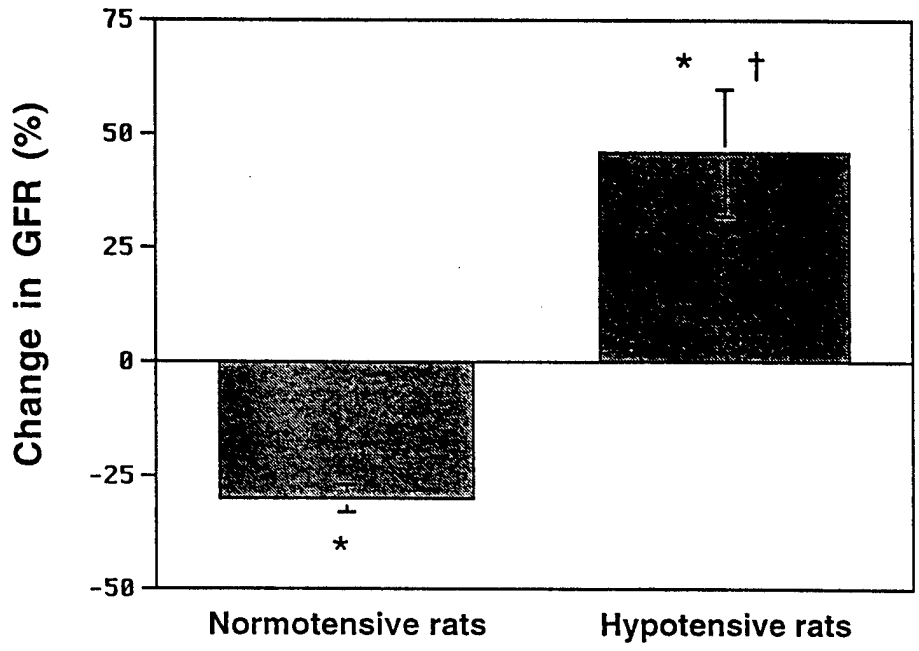
Figure 1



Comparison of the percent increase in MAP induced by L-NAME in normovolemic and hypotensive rats

*=p<0.05 compared to pre-LNAME (baseline) period
†=p<0.05 compared to normovolemic rats
Normotensive rats n=11; hypotensive rats n=10

Figure 2



Comparison of the percent change in GFR induced by L-NAME in normovolemic and hypotensive rats

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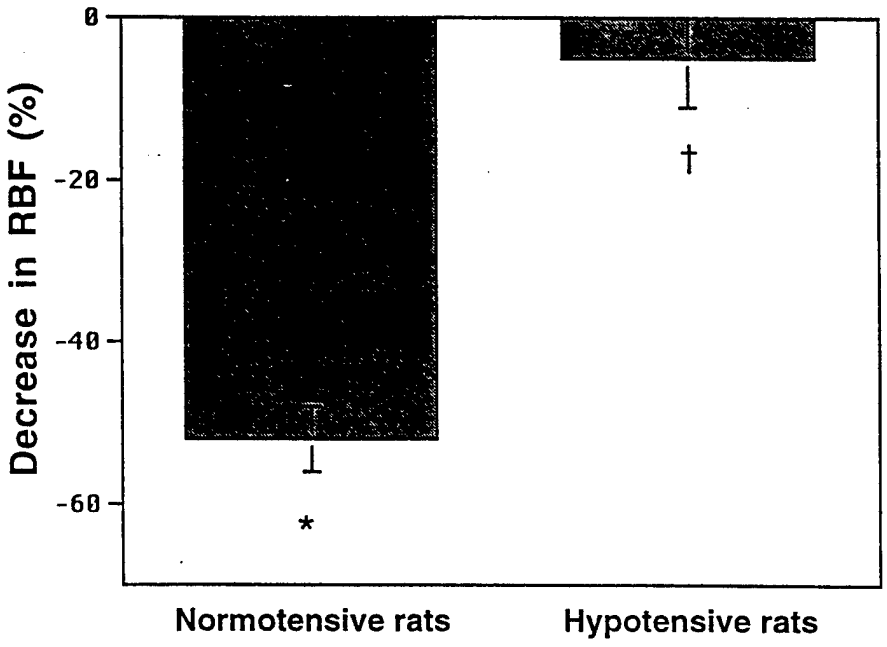
Normotensive rats n=11; hypotensive rats n=10

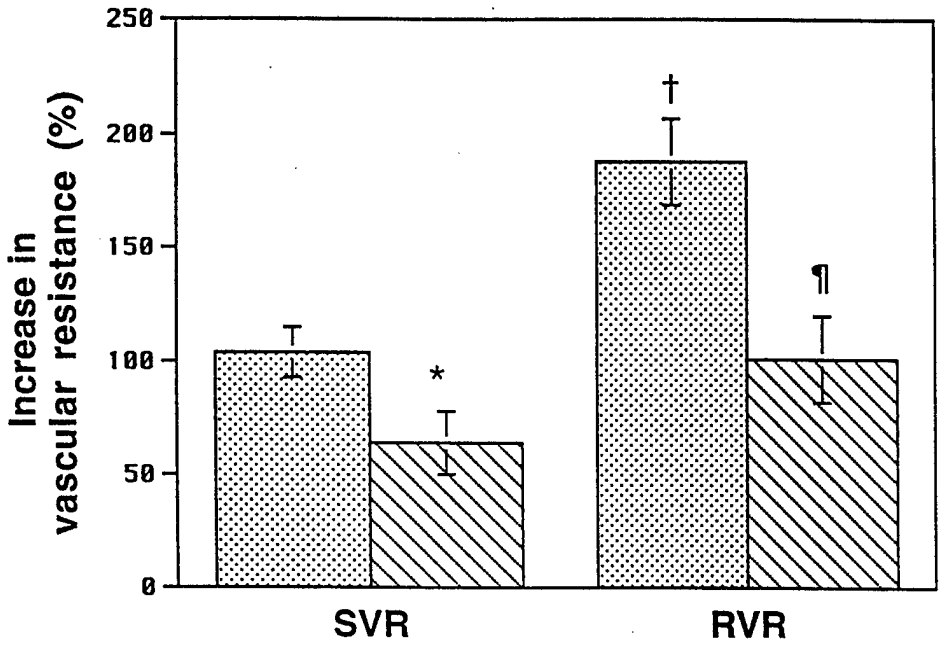
Figure 3



Comparison of the percent change in RBF induced by L-NAME in normovolemic and hypotensive rats

*=p<0.05 compared to pre-LNAME (baseline) period
†=p<0.05 compared to normovolemic rats
Normotensive rats n=11; hypotensive rats n=10

Figure 4



Comparison of the percent change in SVR and RVR induced by L-NAME in normovolemic rats (stippled bar) and hypotensive rats (cross hatched bar)

*=p<0.05 compared to SVR in normovolemic animals
†=p<0.05 compared to SVR in normovolemic animals
¶=p<0.05 compared to RVR in hypotensive animals
Normotensive rats n=11; hypotensive rats n=10